Practitioner's Docket No. MPI98-149P1USRCEM **09/775,803**

REMARKS

Applicants thank the Examiner for entering the amendments filed on March 31, 2003 upon acceptance of the request for continued examination under 37 CFR 1.114.

Applicants have amended the claims 1, 5, 10, 15, 21, 23, and 28-30. A marked-up version of the claims is enclosed herewith. Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 are pending. No new matter has been added.

REJECTION OF CLAIMS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the full scope of the invention. The Examiner argues that the scope of the claims does not enable one skilled in the art to produce a transgenic mouse with a phenotype described in the specification without undue experimentation. The Examiner cites a publication by Kahn, et al. (1999) Blood 94:4112-4121, who produced a transgenic GP V-deficient mouse and did not observe the phenotype reported by Applicants.

The Applicants respectfully traverse the Examiner's rejection. Applicants note that while the target vector constructs between the instant invention and Kahn show some differences, which might result in differences in expression of unrelated genes on the opposite strand from the mouse GP V gene in the mouse genome, both the Applicants and Kahn demonstrated loss of GP V gene expression in the homozygous mice, by protein expression analysis and by mRNA analysis, respectively. Therefore skill in the art and information in the specification is sufficient to produce the genotype of the GP V deficient mouse. Applicants contend that the experimentation Kahn performed to examine the phenotype of that GP V deficient mouse led to insufficient data to conclusively determine the phenotype. Note that, while the Kahn et al. publication of December, 1999 was after the November 15, 1998 published abstract and poster presentation and the November 9, 1999 journal publication of Applicants' invention, Kahn appear to have been unaware of Applicants' results. Thus, Kahn et al. missed the opportunity to be guided by Applicants to observe the phenotype produced by the instant invention.

A review comparing the experimental results of Applicants and Kahn leads Applicants to argue that the phenotype produced by Kahn is the same. Several phenotypic similarities between Applicants' invention and Kahn's mouse are evident from the results presented by both: GP Ib-IX complex is

[illegible] specification [illegible]

remaining studies, results of which appear to conflict, reviews the properties being measured and the

statistical significance of the assays. Platelet aggregation and bleeding time were measured in both studies. For platelet aggregation Kahn performed three experiments with 3-4 mice each. Applicants performed five experiments of 6-10 mice each. For bleeding time, Kahn tested 45 mice, but Applicants tested 285 mice and performed further statistical analysis of the results. It is known in the art that mice of the F2 generation, the mice used for both studies, have variable phenotypes due to ongoing chromosome segregation. As a result, statistical analysis of phenotypes is essential, with a general accepted standard of a minimum of 30 mice required to interpret phenotypes. The remaining data, on ATP secretion (Kahn et al.) and fibrinogen binding (Applicants) test different aspects of platelet activation (release of dense granule contents and activation of gpIIb/IIIa, respectively) using different methods (lumiaggregometry and flow cytometry, respectively). Applicants note that Kahn et al. based conclusions not only on low numbers of mice, but also partially on results using a thrombin concentration (30 nM), which is higher than the 20 nM concentration above which the Applicants concluded no difference was detectable among phenotypes (page 23, lines 4-5). Applicants believe that the performance of studies to their statistically significant endpoints is not undue experimentation, just repetition of standard techniques known in the art.

However, in order to expedite prosecution of the present application, Applicants have amended claims 1, 5, 10, 15, 21, 23, and 28-30 to describe the claimed transgenic mouse as having the phenotype of decreased bleeding time. Support for this amendment can be found in the specification at, for example, page 6 line 21 and the experimental results of Example 6, page 24, lines 5-6. This phenotype distinguishes the mouse of the invention from the description of Kahn et al. In view of this amendment and the reasons stated above, Applicants respectfully request this rejection be withdrawn.

REJECTION OF CLAIMS UNDER 35 U.S.C. §103

Claims 1, 2 (or 3?), 5, 8, 10, 23, 24, 26, and 27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Moreadith et al. (J. Mol. Med. 75:208-216) taken with Dong et al. (Blood 89:4355-4363) in further view of Ravanat et al. (Blood 89:3253-3262). Moreadith teaches making and using knockout mice, Dong teaches inserting the gene for GPV and characterizing the GP V gene on the high affinity thrombin receptor and Ravanat teaches cloning of the mouse GP V gene. The Examiner states that using the combination of the teachings, one would have been motivated to make a GP V knockout mouse and use them to study the role of GP V in the GP Ib-IX-V complex. Applicants respectfully traverse the rejection.

(A[illegible] for [illegible] the statements by Dong which teach away from the motivation to [illegible]

example, on page 4362, last paragraph, Dong states that these studies must be performed in a way in which the cleavage of GP V can be manipulated and the end point of thrombin's action on this

polypeptide is not obscured by the presence of the seven-transmembrane-domain receptor." Specifically, on platelets, more than one thrombin receptor exists to contribute to any results and manipulation of cells in isolation is preferred. Dong teaches that studying GP V function in something as complex as a mouse and/or a mouse platelet having both GP Ib-IX-V and the seven transmembrane thrombin receptor, among other mediators of thrombin activity, would not result in any meaningful conclusions on the function of GP V.

Another reason for traversal is that Applicants have amended claims 1, 5, 10, 23 (claims 3, 8, 24, 26 and 27 dependent thereon) to recite that the resulting mouse have a decreased bleeding time. Neither Dong et al. nor Ravenat et al. teach this result. Both invoke the Bernard-Soulier syndrome, a disorder characterized by increased bleeding time, as a possible phenotype for reduced or absent GP V functionality. In addition, Ravenat hypothesizes that a lack of GP V would inhibit the platelet response to thrombin (page 3260). These phenotypes are opposite to the phenotype observed by Applicants (Examples 5-6, pages 22-24 of specification). Therefore, the invention claimed by Applicants produces an unexpected result not taught in the combination of references cited by the Examiner. In view of these amendments and for these reasons, Applicants request that this rejection be withdrawn.

CONCLUSION

The foregoing amendments and remarks are being made to place the Application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims.

This paper is being filed timely within the three month period for response. No extensions of time are required. In the event any extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Respectfully submitted,

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